Human research ethics — a work in progress

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Ethical issues are constantly changing as clinical research and practice push out the boundaries of what we know and do

The beginnings of ethical and regulatory oversight of the human research enterprise are customarily traced to the Nuremberg Code, a set of principles and standards for medical experiments outlined by the Nuremberg war crimes tribunal in 1947 following revelations of the infamous Nazi experiments conducted during World War II.[1] Ironically, Germany was the first Western country to officially require informed consent for non-therapeutic research. In 1900, the Prussian minister for religious, educational and medical affairs issued a directive after it came to light that Albert Neisser had injected syphilitic serum into prostitutes without their knowledge or consent;[2] and in 1931, the Reich Minister of the Interior introduced *Guidelines on innovative therapy and scientific experimentation* following an inquiry into the Lübeck disaster, in which 75 infants died and 168 others developed tuberculosis after receiving a contaminated batch of oral BCG vaccine.[3,4]

In 1964, after more than a decade of drafting, the World Medical Association (WMA) issued the Declaration of Helsinki, elaborating on the basic principles in the Nuremberg Code.[5] This was ratified in Australia the following year, and in 1966 the National Health and Medical Research Council (NHMRC) issued its first *Statement on human experimentation*.[6] The requirement for ethical approval of NHMRC grant applications in 1973 and the addition of *Supplementary Note 1* in 1976, defining the role and functioning of human research ethics committees (HRECs),[6] marked the beginning of the current ethics oversight system in Australia.

The devolution of responsibility for evaluation and approval of clinical trials from the Therapeutic Goods Administration (TGA) to local HRECs and the rapid growth of multicentre trials during the 1990s highlighted a number of weaknesses in the system, particularly the requirement for each HREC to give separate consideration to projects involving research in more than one institution.[7] Recognising these issues, as well as the importance of applying ethical principles to all types of human research, the NHMRC released a significantly revised *National statement on ethical conduct in research involving humans* in 1999.[8]

Subsequently, concern that HRECs have become overburdened with management and regulatory functions that are primarily the responsibility of research institutions has generated discussion of the notion of "research governance", defined as an organisational framework through which institutions are held accountable for maintaining standards of quality, safety, privacy, risk management and financial management of research, in addition to ensuring its ethical acceptability.[9,10] Despite concerns about the risk of creating a massive new bureaucracy,[11] the concept has been enthusiastically embraced[12] and the 2007 revision of the NHMRC national statement has an entire section devoted to governance.[13]

The publication in this issue of the Journal (*page 649*) of a survey of current knowledge of research governance by Babl and Sharwood[14] is thus particularly timely. Researchers, students and clinicians were asked about their familiarity with "the essential national and international documents guiding GCRP" (good clinical research practice), namely the Declaration of Helsinki,[5] the NHMRC national statement[13] and *Australian code for the responsible conduct of research*.[15] The results appear to show a worrying lack of familiarity with the content of some of these "key" documents, and Babl and Sharwood conclude that institutions are failing in their responsibility to provide adequate training for those engaged in research.

Few would disagree that more resources should be devoted to training; however, the study probably overestimates the depth of ignorance. Babl and Sharwood seem unaware that formal guidelines for GCRP were originally published by the TGA in 1991 and superseded in 2000[16] by the *Note for guidance on good clinical practice*, a quality standard agreed to by the International Conference on Harmonization for the design, conduct, recording and reporting of clinical trials.[17,18] While it is essential that principal investigators running clinical trials are familiar with its contents, it is of little relevance to students, researchers and clinicians not directly engaged in drug trials.

As for the Declaration of Helsinki,[5] this is no longer considered a key document. The sixth edition released in 2000 created a worldwide furore centred on two paragraphs, one concerning use of placebos in clinical trials, and the other asserting participants' right of access to the best-proven treatment identified by the trial. Influential American and European regulatory bodies refused to accept the revisions, forcing the WMA to water down the offending paragraphs.[19] As a consequence, the Declaration of Helsinki has declined in moral force and influence. Whereas in 1999, the NHMRC national statement listed it as a relevant publication,[8] in the 2007 revision, it is relegated to a historical reference in the preamble.[13]

Also in this issue of the Journal (*page 653*), Ballantyne and Rogers report their survey of chairs of Australian HRECs on the fair inclusion of men and women in clinical research.[20] They correctly point out that, historically, women have been excluded from clinical trials, resulting in inadequate data on safety and efficacy of marketed drugs, and their findings suggest a lack of awareness, concern and action on the part of HREC chairs.

Following the thalidomide tragedy in the 1960s, there was major strengthening of the drug regulatory agencies in the United States, United Kingdom, Europe and Australia. At that time, in the absence of widespread use of effective means of contraception, there were justifiable ethical concerns about enrolling women of childbearing potential in clinical trials. Exclusion was commonplace until the late 1980s, when the increasingly powerful HIV/AIDS lobby pressured the US Food and Drug Administration into reviewing its drug approval policies.[21] By 1990, the US National Institutes of Health (NIH) had introduced guidelines covering the inclusion of women in clinical trials, strengthened by legislation in 1993, and the most recent policy update in 2000 stated: "NIH experience has indicated that inclusion has been accomplished".[22]

In Australia, a Women and Clinical Trials Working Party was established in 1995 to advise on changes to NHMRC guidelines,[23] and its recommendations were incorporated into the 1999 National Statement,[8] albeit in rather general terms. Ballantyne and Rogers are critical of this, believing that "HRECs require further instruction from

the NHMRC about how to interpret and apply the generic principle of fair inclusion." However, detailed instructions were, in fact, provided in the *Human research ethics handbook*, issued by the NHMRC in 2002.[24] The fact that chairs of HRECs may not be aware of them probably indicates that unfair sex discrimination in clinical trials is no longer a significant issue.

So, where to next in the field of human research ethics? Times have changed. With the increase in off-label prescribing in paediatric practice, our challenge now lies in ensuring that children are adequately represented in clinical trials — with responsibility shared by researchers, sponsors, HRECs and regulators. Human research ethics is a work in progress, and will remain so for the foreseeable future.

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